

REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and the reasons that follow.

Status of the Claims

Claims 80-81 are canceled without prejudice or disclaimer.

Claim 64 is amended to recite specific embodiments and address the § 112 rejections. Specifically, claim 64 is amended to recite that the matrix composition does not comprise polyethylene glycol 2000 monostearate or polyethylene glycol 400 monostearate as taught, for example, at page 9, lines 6-8 of the specification as filed. Claim 64 also is amended to recited embodiments where the coating has two openings. Support for this amendment can be found at page 14, lines 9-11, of the specification as filed.

Applicant adds new claims 82-88 to recite specific embodiments of the matrix composition. New claims 82-87 recite molecular weight ranges for components of the matrix composition, as taught at page 18, line 25, to page 19, line 6, of the specification as filed and in original claim 33. New claim 88 recites specific embodiments of opioids. Support for this claim is found in original claim 13.

These amendments are being made without prejudice or disclaimer. Applicant reserves the right to pursue any canceled subject matter in one or more continuing applications.

Upon entry of these amendments, claims 64-66, 69-79 and 82-88 will be pending. These claims are presented for reconsideration.

The Office Action

Applicant notes with appreciation that all previous rejections have been overcome. Applicant addresses the new rejections below.

Rejections under § 112, First Paragraph

The Office Action rejects claim 64 and dependent claims 65-66 and 69-81 as allegedly failing to comply with the written description requirement. Specifically, it is the Office's

position that while there is support in the specification for a coating that is “substantially insoluble” in aqueous media, there is no support for a coating that is “insoluble” as previously recited. See Office Action at page 4.

Without acquiescing to the propriety of this rejection, Applicant has amended claim 64 to revert to the original “substantially insoluble” language. Applicant notes that there is nothing inherently indefinite about this term, and that the skilled artisan reviewing the present specification would have readily understood what the claimed phrase “substantially insoluble” means when read in the context of the pending claims. For example, the specification teaches matrix coatings that exhibit this property, and polymers suitable for making such coatings. See page 32, line 28, to page 33, line 2, and page 34, lines 12-16, of the specification as filed. Moreover, the use of a coating for a controlled release pharmaceutical composition that is substantially insoluble in and impermeable to aqueous media is common in the art, and will be readily understood by the skilled artisan. Applicant therefore believes that the new matter rejection is overcome, and that claim 64 as amended satisfies the requirements for definiteness.

Rejections under §112, Second Paragraph

The Office Action states that claim 64 is indefinite for reciting a matrix composition that does not comprise a surface active agent, when certain polymers recited as components of the matrix composition are known surfactants. Office Action at page 4.

Without acquiescing to the propriety of this rejection, Applicant has amended claim 64 to more clearly specify the components excluded from the matrix composition. In particular, the claim now excludes PEG 400 monostearate and PEG 2000 monostearate, as taught at page 9, line 7, of the specification as filed. Because amended claim 64 now more clearly recites the excluded polymers Applicants believe the indefiniteness rejection is overcome and should be withdrawn.

Rejections under §103

The Office Action sets forth four separate obviousness rejections which are addressed in turn below.

Non-Obviousness over Rao

The Office Action alleges that claims 64-66 and 79-81 are unpatentable over Rao (U.S. 2003/0203055). While the Office admits that Rao does not teach an opioid in a controlled release polymer matrix that is coated with an insoluble or impermeable polymeric coating, the Office Action states that it would have been obvious for the skilled artisan to modify Rao's composition to use an opioid in place of the disclosed active ingredient. However, even if Rao was modified in such a manner, it would not result in the claimed composition.

As reflected in independent claim 64, the instant claims are directed to methods for treating a patient suffering from pain that is sensitive to an opioid comprising orally administering an opioid in a controlled release pharmaceutical composition comprising a matrix composition comprising (a) a polymer or a mixture of polymers, (b) an opioid, and optionally, (c) one or more pharmaceutically acceptable excipients. The matrix is provided with a coating that is substantially insoluble in and impermeable to aqueous media and comprises one or more polymers selected from a recited list. The composition of the claimed method comprises a coating that has two openings and exposes at least one surface of the matrix, thereby allowing controlled release of the opioid by erosion of the matrix surface.

Rao does not teach or suggest the recited compositions. Moreover, the composition disclosed in Rao has a different structure and mechanism of drug release than the recited compositions. Thus, it would not lead the skilled artisan to the claimed methods.

Rao teaches a method for treating visceral pain syndrome. Example 6 cited in the Office Action discloses a sustained release dosage form containing an active ingredient and a pharmaceutically acceptable carrier which is coated with a wall. More specifically, Rao teaches a sustained release dosage form containing an active ingredient and a pharmaceutically acceptable carrier surrounded by an interior wall and an exterior wall having an exit. See para [0272].

Nowhere does Rao teach or suggest a composition in which the coating layer surrounding the active ingredient-carrier mixture has two openings as claimed. Moreover, Rao does not teach the release of the active agent from the disclosed composition to occur by erosion of the matrix surface as claimed. Rather, release of the active agent from Rao's composition occurs by osmotic pump action.

For example, in paragraph [0275], Rao states that, “the coat includes a passage former that leaves the coat in the presence of fluid, and a wall surrounds the coat and prevents lipid in the gastrointestinal tract from entering the dosage form.” That is, Rao teaches a composition in which water from the GI tract enters through a semi-permeable wall and dissolves passage-formers in the coat, thus allowing water to enter the matrix and drive the active agent out of the matrix.

In sharp contrast, the claimed compositions have two openings in the coat surrounding the matrix. As described in the specification and recited in the claims, the recited compositions achieve controlled drug release by erosion of the matrix, such as by the aqueous biological milieu. Thus, not only do the inventive compositions differ structurally from the composition disclosed in Rao, but they also differ in the underlying mechanism by which controlled release of drug is achieved.

For at least the foregoing reasons, the Office is respectfully requested to withdraw the rejection over Rao.

2. *Non-Obviousness over Wong in view of Rao*

The Office Action alleges that claims 64-66 and 79-81 are unpatentable over Wong (U.S. 4,824,675) in view of Rao. Applicants respectfully traverse.

Wong teaches a dispenser for delivering tiny pills to an environment of use, such as in the GI tract. According to Wong, the dispenser consists of an internal lumen that contains a carrier means consisting of a carrier and tiny pills of the active agent, which carrier means is surrounded by a wall. See, for example, col. 6, lines 5-7. A passageway or opening connects the outside of the dispenser with the lumen. *Id.*

The Office appears to equate the wall of Wong’s dispenser with the coating of the recited composition, but it must be understood that Wong’s wall is separate from its tiny pills, not a coating that is applied to the pills. Thus, the disclosed wall does not read and in no way relates to the recited coating.

The Office cites Example 7 of Wong in support of the section 103 rejection, but this embodiment of Wong in no way suggests the claimed invention. The tiny pills of Example 7 are

comprised of an active agent core surrounded by cellulose acetate. The pill does not include any type of matrix, let alone a matrix as recited here. The tiny pills are then immersed in a matrix comprising cellulose acetate, polyethylene oxide and hydroxypropylmethyl cellulose. See Wong at column 22, lines 37-39. The pill-containing matrix is then provided with a wall that comprises cellulose acetate. Thus, the cited example discloses an outer wall surrounding a matrix that has dispersed therein tiny pills comprised of a drug (only) core provided with a cellulose acetate coating. This is a far cry from Applicant's coated matrix compositions.

Moreover, Wong's dispenser has a single opening (mouth 13), whereas the instant claims recite compositions comprising a coated matrix, wherein the coating has two openings.

In summary, the device disclosed in Wong has a different structure and mechanism of drug release than the recited compositions. Thus, it would not lead the skilled artisan to the claimed methods.

For the reasons set forth above, combining Rao with Wong does not remedy the deficiencies of Wong. That is, the combination of references does not suggest a composition as claimed, let alone the recited methods.

Claim 64 and the claims that depend therefrom are therefore are patentable over the combined teachings of Wong and Rao, and the Office is respectfully requested to withdraw the obviousness rejection.

3. *Non-Obviousness over DePrince in view of Rao*

The Office Action alleges that claims 64-66 and 79-81 are unpatentable over DePrince (U.S. 4,898,733) in view of Rao. Applicants respectfully traverse.

DePrince teaches a layered, compression molded device for the sustained release of an active agent. The disclosed device consists of a body fluid contacting layer that is compression molded onto a non-body fluid contacting layer containing the active agent. See Abstract and col. 5, lines 44-45. An outer barrier layer made of an impermeable material surrounds the inner two layers.

DePrince's three layered system does not teach or suggest the claimed composition comprising an active agent matrix surrounded by a coating layer. That is, the disclosed device

does not structurally read on the claimed compositions. The differences between the claimed compositions and those of DePrince are underscored by their different deliver profiles. For example, DePrince's composition does not exhibit zero order release. Moreover, as illustrated in Figure 4, only 75% drug is released after a 35 day study period.

Combining Rao with DePrince does not remedy the deficiencies of DePrince, for the reasons set forth above. That is, neither DePrince nor Rao teach or suggest a composition as claimed. Thus, the combination of DePrince and Rao does not support a *prima facie* case of obviousness. Applicant therefore respectfully requests the withdrawal of the obviousness rejection.

4. *Non-Obviousness over Rao in view of Sackler*

Claims 69-78 are rejected for alleged obviousness over Rao in view of Sackler (U.S. 5,478,577). Applicants respectfully traverse.

Sackler is cited for allegedly teaching a method for effective pain management using an oral dosage formulation that is capable of achieving the pharmacokinetic profiles recited in claims 69-78. According to the Office, combining Rao with Sackler makes it obvious to formulate an opioid in Rao's composition and makes it obvious to achieve the recited pharmacokinetic profiles. Applicants respectfully traverse.

While Sackler teaches that certain drug delivery profiles may be desirable, it does not teach or suggest that the disclosed delivery profiles could be achieved using Rao's composition. Thus, there is no rational basis for the obviousness rejection.

As shown above, Rao does not teach or suggest a composition as recited in the instant claims. Sackler does not remedy this deficiency, as it also fails to teach or suggest a composition as claimed, comprising a matrix and a coating as claimed. Thus, the combination of Sackler and Rao does not make out a case of *prima facie* obviousness.

Applicant therefore respectfully requests that this rejection be withdrawn.

CONCLUSION

Applicant believes that the application is in condition for allowance, and favorable reconsideration is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance prosecution, or if any issues remain that might be resolved by telephone.

Respectfully submitted,

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By Courtenay C. Brinckerhoff

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 295-4094
Facsimile: (202) 672-5399

Courtenay C. Brinckerhoff
Attorney for Applicant
Registration No. 37,288

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, then the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.